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A FACILE ONE-POT SYNTHESIS OF BENZO[*b*]BENZOFURO- AND BENZO[*b*]BENZOTHIENO[3,2-*h*][1,6]NAPHTHYRIDINES

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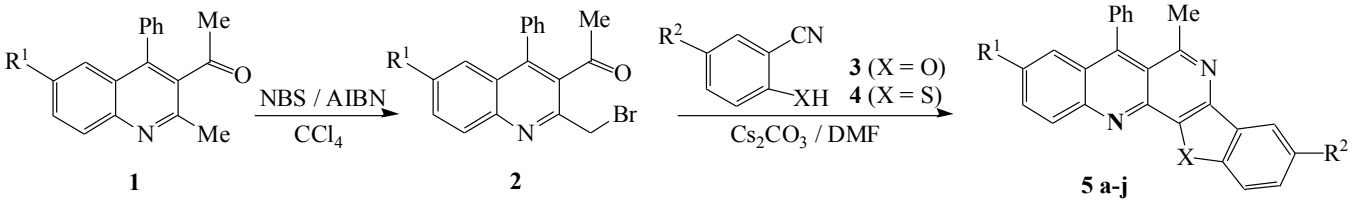
Abstract – An efficient domino protocol for the synthesis of benzo[*b*]benzofuro- and benzo[*b*]benzothieno[3,2-*h*][1,6]naphthyridines (**5**) was described. The construction of this new pentacyclic system was achieved undergo a tandem Thorpe-Ziegler-type heterocyclization of 3-acetyl-2-bromomethylquinolines (**2**) with salicylonitriles (**3**) or 2-mercaptobenzonitrile (**4**) in one-pot with good yields.

Quinolines, naphthyridines and their polycyclic derivatives are an important pharmacophore present in many natural[1] and designed synthetic products of therapeutic applications. They are associated with a wide spectrum of biological activities such as anticancer,[2] anti-HIV-1,[3] and cytotoxic activity. [4] Therefore, the synthesis of naphthyridine derivatives has aroused great interest in organic and medicinal communities.[5]

On the other hand, the carbon-carbon and carbon-heteroatom bond-forming reactions are crucial to organic synthesis. Domino processes are important for generating high levels of diversity and complexity giving rise to complex structures by simultaneous formation of two or more bonds from simple substrates. These advantages are of particular interest in pharmaceutical research for the construction of libraries of biologically active compounds. Thus, developing new, environmentally benign domino reactions is an important topic of green chemistry.[6]

We have been engaged in the development of economical syntheses of heterocyclic systems,[7] herein, we provide a novel approach to prepare a series of benzo[*b*]benzofuro- and benzo[*b*]benzothieno[3,2-*h*][1,6]-naphthyridines *via* Thorpe-Ziegler-type heterocyclization (Scheme 1).[8]



Scheme 1. Synthesis of benzo[*b*]benzofuro- and benzo[*b*]benzothieno[3,2-*h*][1,6]naphthyridines

3-Acetyl-2-methyl-4-phenylquinolines (**1a**, **b**) as starting materials, which were easily obtained by condensation of *o*-aminobenzophenone with pentanedione and citric acid under solvent free conditions,[9] were treated with *N*-bromosuccinimide to give 3-acetyl-2-bromomethyl-4-phenylquinolines (**2a**, **b**) in 83 and 88% yields, respectively.

Initially, 3-acetyl-2-bromomethyl-4-phenylquinoline (**2a**) and salicylonitrile (**3**) were selected as the model substrates (Table 1). Several bases were screened, and Cs_2CO_3 was relatively efficient with 84% yield of **5a** (entry 2). K_2CO_3 and *t*-BuOK behaved less successfully (entries 1 and 3), while KOH gave the product in relatively low yield (entry 4). Solvent was investigated and DMF was found to be more effective than DMSO, NMP, and MeCN (entries 5-7). Moreover, the yield decreased at 80 °C and 120 °C (entries 8 and 9). Finally we found the reaction was most efficient when conducted with Cs_2CO_3 in DMF at 100 °C. The structure of 13-methyl-14-phenylbenzo[*b*]benzofuro[3,2-*h*][1,6]naphthyridine **5a** was supported by the spectral data as well as the elemental analysis ($C_{25}H_{16}N_2O$) data. Thus, the ^{1}H NMR spectrum shows signals at δ 7.48-7.68 (m, 9H), 7.90-7.91 (m, 2H), 8.34-8.35 (m, 1H), 8.49 (d, J = 8.8 Hz, 1H) for benzene nucleus protons and singlet peak for the methyl at δ = 2.48.

Table 1. Optimization of reaction conditions on the synthesis of **5a** *

Entry	Base	Solvent	Temp (°C)	Time (h)	Yield (%)
1	K_2CO_3	DMF	100	13	68
2	Cs_2CO_3	DMF	100	9	84
3	*t*-BuOK	DMF	100	10	72
4	KOH	DMF	100	10	54
5	Cs_2CO_3	DMSO	100	10	70
6	Cs_2CO_3	NMP	100	10	74
7	Cs_2CO_3	MeCN	reflux	24	38
8	Cs_2CO_3	DMF	80	12	65
9	Cs_2CO_3	DMF	120	8	80

* Reaction conditions: **2a** (1.0 equiv), **3** (1.0 equiv), base (3.0 equiv), solvent (20 mL).

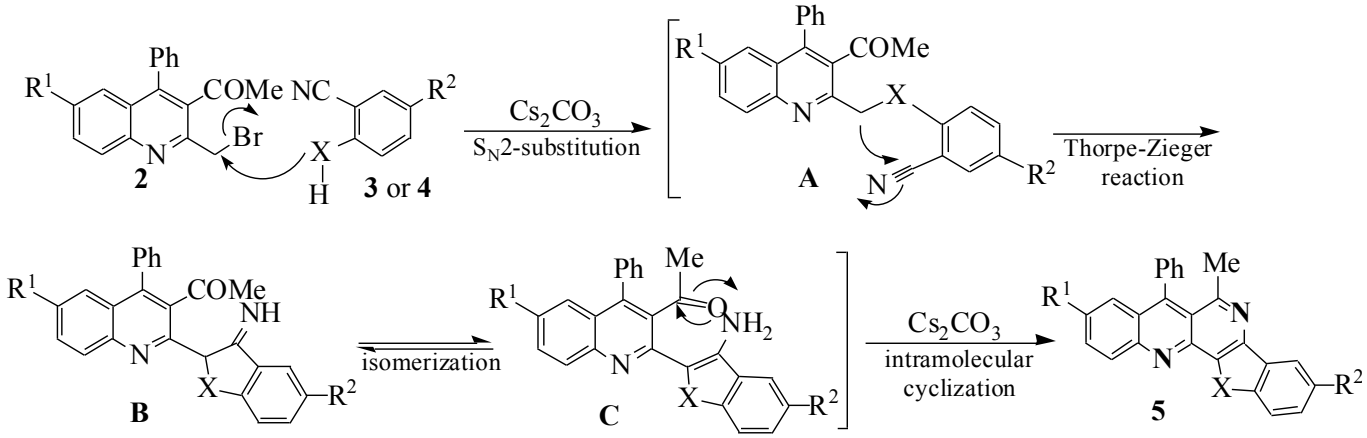
With the optimized conditions in hand, the scope and generality of this novel synthesis of benzo[*b*]benzofuro[3,2-*h*][1,6]naphthyridines (**5a-h**) were studied. As shown in Table 2, not only salicylonitrile but also 5- methoxy, 5-chloro, and 5-bromo substituent worked well (entries 1-8).

To expand the scope of the current method, 2-mercaptobenzonitrile was examined as a replacement for salicylonitrile to synthesize benzo[*b*]benzothieno[3,2-*h*][1,6]naphthyridines. The desired products (**5i, 5j**) were also successfully obtained with good yields (Table 2, entries 9 and 10).

Table 2. Synthesis of benzo[*b*]benzofuro- and benzo[*b*]benzothieno[3,2-*h*][1,6]naphthyridines **5**

Entry	Products	R^1	R^2	X	Time (h)	Yield (%)
1	**5a**	H	H	O	9	84
2	**5b**	H	OMe	O	8	79
3	**5c**	H	Cl	O	12	68
4	**5d**	H	Br	O	12	70
5	**5e**	Cl	H	O	9	78
6	**5f**	Cl	OMe	O	8	80
7	**5g**	Cl	Cl	O	12	72
8	**5h**	Cl	Br	O	11	74
9	**5i**	H	H	S	7	85
10	**5j**	Cl	H	S	7	80

The proposed mechanism of the process is summarized in Scheme 2. The present synthetic sequence was initiated by an alkylation of 3-acetyl-2-bromomethylquinolines **2** with salicylonitriles (**3**) or 2-mercaptobenzonitrile (**4**) giving to the ethers **A**. An intramolecular carbanion addition across the nitrile was brought about by ethers **A** *via* Thorpe-Ziegler reaction, and isomerization, resulting in the formation of 3-amino-2-benzofurans (or 3-amino-2-benzothiophenes) **C**. Next, this then undergoes intramolecular cyclization to yield the pentacyclic products **5**.



Scheme 2. Proposed reaction mechanism for the formation of compound **5**

In conclusion, we have developed an efficient domino protocol for the synthesis of benzo[*b*]benzofuro- and benzo[*b*]benzothieno[3,2-*h*][1,6]naphthyridines *via* Thorpe-Ziegler-type heterocyclization in one-pot with good yields. This method has the advantages of readily available starting materials, mild reaction conditions, and operational simplicity.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The NMR spectra were recorded with a Bruker Avance 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using TMS an internal reference. IR spectra were measured on Shimadzu FTIR-8300 spectrophotometer. C, H, and N analyses were performed by a HP-MOD 1106 microanalyzer. The preparation of 3-acetyl-2-methyl-4-phenylquinolines (**1**) was according to the literature procedure.[9] All other chemicals used in this study were commercially available.

Preparation of 3-acetyl-2-bromomethyl-4-phenylquinolines (2). To a solution of 3-acetyl-2-methyl-4-phenylquinoline (**1**) (5.0 mmol) in carbon tetrachloride (150 mL) containing azodiisobutyronitrile (AIBN) (100 mg) was added *N*-bromosuccinimide (NBS) (5.0 mmol) and refluxed for 5 h. After the reaction mixture was cooled, it was diluted with water (50 mL). The extract was dried over sodium sulfate and evaporated in vacuo to leave a residue which was recrystallized from isopropanol to give **2a**, **b**.

3-Acetyl-2-bromomethyl-4-phenylquinoline (2a): Red needles. mp 133-135 ºC; IR (KBr, cm^{-1}): *v* 1667 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.04 (s, 3H, CH_3), 4.88 (s, 2H, $BrCH_2$), 7.41-7.42 (m, 2H), 7.54-7.56 (m, 4H), 7.71 (d, J = 8.4 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 31.8, 32.9, 125.8, 126.2, 127.9, 128.9, 129.2, 129.6, 130.0, 130.6, 133.9, 135.0, 145.6, 147.1, 152.9, 205.3. *Anal*. Calcd for $C_{18}H_{14}BrNO$: C 63.55, H 4.15, N 4.12. Found: C 63.67, H 4.24, N 4.20.

3-Acetyl-2-bromomethyl-6-chloro-4-phenylquinoline (2b): Red needles. mp 165-167 ºC; IR (KBr, cm^{-1}): *v* 1672 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.02 (s, 3H, CH_3), 4.84 (s, 2H, $BrCH_2$), 7.38-7.39 (m, 2H), 7.58-7.59 (m, 3H), 7.65 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 8.06-8.07 (m, 1H,). ^{13}C NMR ($CDCl_3$): δ 32.1, 33.3, 124.9, 126.7, 129.5, 130.1, 130.2, 131.8, 132.0, 133.4, 134.1, 134.8, 145.1, 145.2, 153.3, 204.2. *Anal*. Calcd for $C_{18}H_{13}BrClNO$: C 57.70, H 3.50, N 3.74. Found: C 57.81, H 3.63, N 3.82.

Typical Procedure for the Preparation of Benzo[*b*]benzofuro- and Benzo[*b*]benzothieno[1,6]-naphthyridin-5(6*H*)-ones. To a solution of 3-acetyl-2-bromomethyl-4-phenylquinoline (**2**) (1.0 mmol) in DMF (20 mL) was added salicylonitrile (**3**) or 2-mercaptobenzonitrile (**4**) (1.0 mmol) and cesium carbonate (3.0 mmol). The mixture was heated at 100 °C (monitored by TLC). At the end of the reaction, the reaction mixture was cooled to rt, and then water (30 mL) was added to the mixture and stirred for 30 min. The solid was filtered and recrystallized from HOAc to afford the corresponding products **5a-j**.

13-Methyl-14-phenylbenzo[*b*]benzofuro[3,2-*h*][1,6]naphthyridine (5a): Red needles. mp 265-267 ºC;

^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H, CH_3), 7.48-7.68 (m, 9H), 7.90-7.91 (m, 2H), 8.34-8.35 (m, 1H), 8.49 (d, J = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 29.1, 112.7, 119.7, 120.6, 123.8, 124.2, 126.3, 126.8, 127.8, 128.1, 128.5, 128.9, 129.4, 129.6, 132.2, 135.9, 138.4, 139.9, 143.0, 149.9, 150.9, 156.8, 158.7. *Anal*. Calcd for $C_{25}H_{16}N_2O$: C 81.31, H 4.47, N 7.77. Found: C 81.43, H 4.56, N 7.83.

9-Methoxy-13-methyl-14-phenylbenzo[*b*]benzofuro[3,2-*h*][1,6]naphthyridine (5b): Red needles. mp 249-251 ºC; ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 7.21 (d, J = 8.4 Hz, 1H), 7.49-7.60 (m, 4H), 7.68-7.80 (m, 5H), 7.93-7.94 (m, 1H), 8.49 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 29.2, 56.0, 101.9, 111.4, 117.3, 119.6, 121.7, 124.6, 126.3, 126.8, 128.1, 128.5, 128.9, 129.3, 129.5, 132.2, 138.4, 140.0, 143.7, 149.9, 150.8, 151.6, 156.7, 158.4. *Anal*. Calcd for $C_{26}H_{18}N_2O_2$: C 79.98, H 4.65, N 7.17. Found: C 80.12, H 4.73, N 7.25.

9-Chloro-13-methyl-14-phenylbenzo[*b*]benzofuro[3,2-*h*][1,6]naphthyridine (5c): Red needles. mp $>$ 300 ºC; ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H, CH_3), 7.46-7.66 (m, 8H,), 7.79-7.80 (m, 1H), 7.92-7.93 (m, 1H), 7.24-7.25 (m, 1H), 8.46-8.47 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 29.3, 108.5, 113.7, 119.9, 120.3, 122.0, 125.7, 126.9, 127.8, 128.1, 128.6, 128.9, 129.3, 129.5, 129.6, 132.3, 138.2, 139.7, 144.0, 149.8, 150.9, 154.9, 159.2. *Anal*. Calcd for $C_{25}H_{15}ClN_2O$: C 76.05, H 3.83, N 7.09. Found: C 76.16, H 3.92, N 7.16.

9-Bromo-13-methyl-14-phenylbenzo[*b*]benzofuro[3,2-*h*][1,6]naphthyridine (5d): Red needles. mp 292-294 ºC; ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 7.48-7.54 (m, 3H), 7.59-7.62 (m, 1H), 7.69-7.78 (m, 5H), 7.93-7.96 (m, 1H), 8.44 (s, 1H) , 8.49 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 28.9, 114.0, 114.2, 117.2, 119.9, 123.7, 123.8, 126.8, 127.0, 127.1, 128.2, 128.7, 129.1, 129.4, 129.5, 130.8, 132.7, 132.8, 138.0, 139.7, 155.4, 158.7, 159.4. *Anal*. Calcd for $C_{25}H_{15}BrN_2O$: C 68.35, H 3.44, N 6.38. Found: C 68.46, H 3.53, N 6.51.

2-Chloro-13-methyl-14-phenylbenzo[*b*]benzofuro[3,2-*h*][1,6]naphthyridine (5e): Red needles. mp 265-267 ºC; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 7.44-7.49 (m, 4H), 7.57-7.67 (m, 4H), 7.80-7.86 (m. 2H), 8.25 (d, J = 8.4 Hz, 1H,), 8.38 (d, J = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 29.0, 112.7, 119.8, 120.7, 123.9, 126.3, 127.2, 128.0, 128.8, 129.0, 129.2, 129.5, 129.8, 131.0, 132.4, 133.4, 137.6, 139.8, 142.7, 148.2, 150.5, 156.8, 158.6. *Anal*. Calcd for $C_{25}H_{15}ClN_2O$: C 76.05, H 3.83, N 7.09. Found: C 76.16, H 3.90, N 7.13.

2-Chloro-9-methoxy-13-methyl-14-phenylbenzo[*b*]benzofuro[3,2-*h*][1,6]naphthyridine (5f): Red needles. mp 287-289 ºC; ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 4.09 (s, 3H, OCH_3), 7.42-7.45 (m, 4H), 7.54-7.62 (m, 4H), 7.83-7.89 (m. 2H), 8.35 (d, J = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 29.5, 56.0, 110.4, 117.5, 120.6, 122.8, 126.7, 127.8, 128.0, 128.6, 129.1, 129.3, 129.5, 129.7, 131.0, 132.5, 133.7, 138.4, 139.2, 142.6, 147.8, 150.9, 157.9, 159.4. *Anal*. Calcd for $C_{26}H_{17}ClN_2O_2$: C 73.50, H 4.03, N 6.59. Found: C 73.59, H 4.16, N 6.64.

2,9-Dichloro-13-methyl-14-phenylbenzo[*b*]benzofuro[3,2-*h*][1,6]naphthyridine (5g): Red needles. mp

＞300 ºC; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 7.45-7.52 (m, 4H), 7.69-7.80 (m, 5H), 8.22 (s, 1H), 8.39-8.40 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 29.1, 113.7, 120.1, 120.5, 125.5, 126.4, 127.4, 128.1, 128.8, 129.3, 129.5, 129.7, 131.0, 132.7, 133.6, 135.3, 137.5, 139.8, 143.8, 148.2, 150.2, 155.0, 159.1. *Anal*. Calcd for $C_{25}H_{14}Cl_2N_2O$: C 69.94, H 3.29, N 6.53. Found: C 70.10, H 3.41, N 6.69.

9-Bromo-2-chloro-13-methyl-14-phenylbenzo[*b*]benzofuro[3,2-*h*][1,6]naphthyridine (5h): Red needles. mp 282-284 ºC; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 7.43-7.51 (m, 2H), 7.66-7.68 (m, 1H), 7.77-7.73 (m, 5H), 7.81-7.83 (m, 1H), 8.37-8.38 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 28.9, 86.3, 110.0, 114.2, 117.1, 120.1, 123.6, 126.4, 127.4, 128.8, 129.3, 129.5, 130.8, 130.9, 132.7, 133.6, 137.4, 139.6, 143.6, 148.2, 150.3, 155.4, 159.2. *Anal*. Calcd for $C_{25}H_{14}BrClN_2O$: C 63.38, H 2.98, N 5.91. Found: C 63.43, H 3.12, N 6.03.

13-Methyl-14-phenylbenzo[*b*]benzothieno[3,2-*h*][1,6]naphthyridine (5i): Red needles. mp 250-252 ºC; ^{1}H NMR ($CDCl_3$): δ 2.83 (s, 3H, CH_3), 7.50-7.51 (m, 2H), 7.82-8.06 (m, 7H), 8.21 (s, 1H), 8.54-8.55 (m, 1H), 8.63-8.67 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 23.7, 110.0, 117.2, 119.4, 119.5, 122.9, 123.6, 124.4, 126.5, 127.5, 127.9, 128.8, 129.8, 130.9, 132.2, 133.2, 139.4, 140.0, 141.7, 141.9, 143.9, 163.2, 171.7. *Anal*. Calcd for $C_{25}H_{16}N_2S$: C 79.76, H 4.28, N 7.44. Found: C 79.37, H 4.41, N 7.56.

2-Chloro-13-methyl-14-phenylbenzo[*b*]benzothieno[3,2-*h*][1,6]naphthyridine (5j): Red needles. mp ＞300 ºC; ^{1}H NMR ($CDCl_3$): δ 2.78 (s, 3H, CH_3), 7.49-7.51 (m, 2H), 7.80-7.91 (m, 5H), 7.97(s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.59-8.65 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 23.2, 117.9, 121.0, 122.9, 123.6, 124.7, 126.4, 127.5, 127.9, 128.6, 129.3, 130.0, 132.4, 132.6, 133.0, 138.7, 139.3, 139.8, 140.5, 141.7, 144.1, 163.3, 170.0. *Anal*. Calcd for $C_{25}H_{15}ClN_2S$: C 73.07, H 3.68, N 6.82. Found: C 73.16, H 3.83, N 6.95.

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